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Extracellular vesicles as new pharmacological targets to treat atherosclerosis

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ABSTRACT

Extracellular vesicles released by most cell types, include apoptotic bodies (ABs), microvesicles (MVs) and exosomes. They play a crucial role in physiology and pathology, contributing to "cell-to-cell" communication by modifying the phenotype and the function of target cells. Thus, extracellular vesicles participate in the key processes of atherosclerosis from endothelial dysfunction, vascular wall inflammation to vascular remodeling. The purpose of this review is to summarize recent findings on extracellular vesicle formation, structure, release and clearance. We focus on the deleterious and beneficial effects of extracellular vesicles in the development of atherosclerosis. The potential role of extracellular vesicles as biomarkers and pharmacological targets, their innate therapeutic capacity, or their use for novel drug delivery devices in atherosclerotic cardiovascular diseases will also be discussed.

1. Introduction

Atherosclerosis is the underlying cause of cardiovascular diseases, which can lead to stroke, myocardial infarction and death. Atherosclerosis is a unique type of chronic inflammatory disease of the large arteries. Damage of arterial endothelial integrity induced by pro-inflammatory factors such as oxidation of the accumulated low-density lipoprotein (LDL) in the sub-endothelial matrix, is the primary initiating event in atherosclerosis. Injury of the arterial wall can disrupt the permeability of the endothelial barrier, reduce nitric oxide (NO) production, and increase expression of pro-inflammatory molecules, including cell surface adhesion molecules, cytokines, and growth factors. Endothelial dysfunction facilitates the recruitment of T-lymphocytes and circulating monocytes to the intima of the arterial wall. The sub-endothelial monocytes differentiate into macrophages and become foam cells by accumulating cell debris and oxidative-modified lipoproteins. These initial atherosclerotic lesions, called "fatty streaks", progress further with the smooth muscle cell migration from media into the intima, smooth muscle cell proliferation, extracellular matrix production, fibrous tissue formation, and lesion calcification, resulting in the formation of mature atherosclerotic plaque. The most advanced and unstable lesions within the intima are characterized by a fibrous cap containing smooth muscle cells and extracellular matrix enclosing a lipid-rich necrotic core that upon rupture leads to thrombosis and major clinical complications, such as myocardial infarction and stroke (Valanti et al., 2014).

Atherosclerosis develops silently for many years before clinical manifestations occur. Early detection of atherosclerotic lesion formation in asymptomatic individuals, may allow measures to prevent the progression of the pathology towards clinical events. The clinically available atheroprotective drugs aim mainly at reducing the level of circulating LDL, increasing high-density lipoprotein (HDL), and attenuating inflammation. However, the cardiovascular risk remains high, along with morbidity, mortality. Therefore identification of unexplored therapeutic targets and new atheroprotective drugs are increasingly needed.

Extracellular vesicle concentrations are increased in patients with cardiovascular risk factors and after cardiovascular events (Rautou et al., 2011b). The purpose of this review is to report the current knowledge regarding the central role of extracellular vesicles as fine-tune regulators in the cardiovascular diseases and the possibility for novel therapeutic targets, as well as biomarkers for atherosclerosis.

2. Extracellular vesicle classification, formation and release

The presence of membrane vesicles in the extracellular space

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Table 1
Classification of different types of extracellular vesicles.

	Apoptotic bodies	Microvesicles	Exosomes
Size	0.5–2 μm	100–1000 nm	20–100 nm
Density (g/ml)	1.16–1.28	1.04–1.07	1.13–1.19
Formation	Cell surface, outward blebbing of apoptotic cell membrane	Cell surface, outward blebbing of cell membrane	Endolysosomal pathway, inward endosomal membrane budding, and multivesicular bodies fusion with cell membrane
Contents	Nuclear fractions, DNA, RNA, microRNA (miRNA), protein, cell organelles	RNA, miRNA, other non-coding RNA, cytoplasmic protein and membrane protein, cell organelles, lipids	RNA, miRNA, other non-coding RNA, cytoplasmic protein and membrane protein, major histocompatibility complex (MHC)
Membrane properties	Membrane permeable (PI positive)	Membrane impermeable (PI negative)	Membrane impermeable (PI negative)
Markers	Annexin V positivity	Annexin V positivity, Origin cell-specific markers	integrins (α3, α4, β1, β2), MFGE8/lactadherin, Tetraspanins family (CD81, CD82, CD9, CD63), ESCRT proteins (alix, TSG101), actin, flotillin, clathrin

PI indicates propidium iodide; MFGE8—milk fat globule-EGF factor8; ESCRT—endosomal sorting complexes required for transport.

was observed as early as in 1960s (Wolf, 1967); however, shedding vesicles were considered for a long time to be inert cellular debris resulting from cell damage or dynamic plasma membrane turnover. It is only recently that major advances have been made in the identification of their biological significance as tools in various pathophysiological settings, including regulating coagulation, angiogenesis, cell survival, modulation of the immune response, and inflammation. Recently, the International Society for Extracellular Vesicles has recommended using the term "extracellular vesicles" as a generic term for all types of vesicles found in the extracellular space.

Extracellular vesicles are particles heterogeneous in size 20 nm–2 μm (Gaceb et al., 2014) enclosed by a phospholipid bilayer, and released into extracellular medium of most cell types via

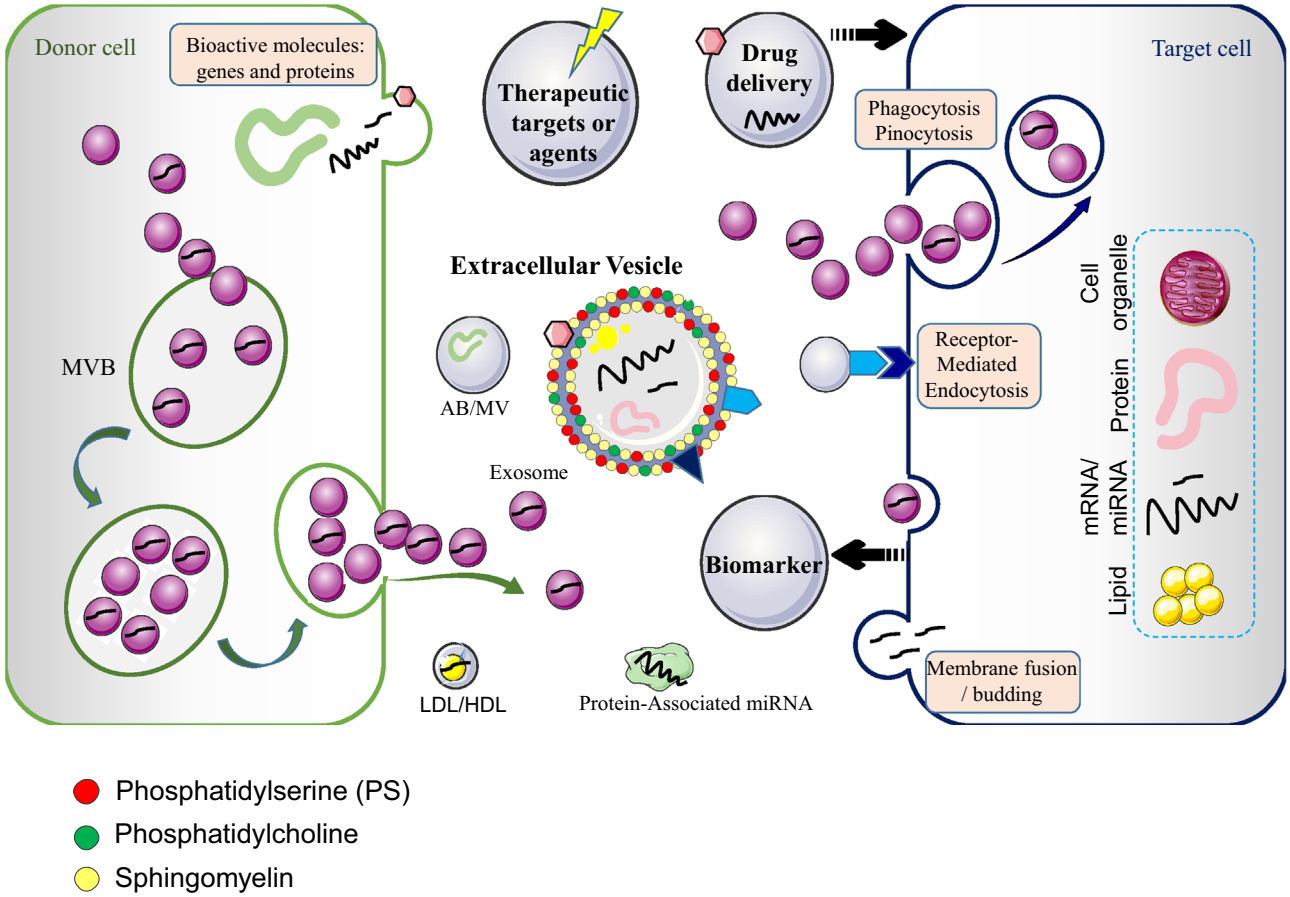

Fig. 1. Role of extracellular vesicles (EVs) in atherosclerosis. Exosomes are formed by the fusion of multivesicular bodies (MVB) with the plasma membrane, whereas both microvesicles (MVs) and apoptotic bodies (ABs) are generated by the outward budding and fission of the cell membrane. All three types of extracellular vesicle carry receptors, ligands, cytoplasmic and membrane proteins, mRNAs, miRNAs. Extracellular vesicles can be regarded as intra-cellular signaling for several core biological processes. Extracellular vesicles maintain cellular homeostasis by delivering their vesicular content to target cells. Endocytosis, phagocytosis, micropinocytosis, or directly cell surface membrane fusion are the major mechanisms in cell extracellular vesicle uptake. In a healthy individual, the formation and clearance of extracellular vesicles are balanced whereas in a patient with atherosclerosis, their formation is likely enhanced and their clearance decreased. This imbalance leads to an increase in the levels of several extracellular vesicle subpopulations which might serve as biomarkers in patients with atherosclerosis. Several anti-atherosclerotic drugs or some dietary nutrients might target extracellular vesicles of different cell origin and show a cardiovascular protective effect. Furthermore, extracellular vesicles offer great potential to serve as pharmacological molecular delivery device. Their content can be modified to contain desired active proteins or genes to target cardiovascular system. MVB indicates multivesicular body; AB, apoptotic body; MV, microvesicle; miRNA, microRNA; LDL, low density lipoprotein; HDL, high density lipoprotein.